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MYERS, C.	

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 11/12/96.

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-43 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1-43 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

15. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Applicants must comply with the requirements of 37 CFR 1.821-1.825 in response to this Office action. In particular, Applicant is required to submit a CRF and paper copy of the Sequence Listing containing the disclosed sequences (see, for example, page 21), an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

16. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 36 is rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. Claim 36 is drawn to an RNA probe comprising ribonucleotides arranged in a sequence which is complementary to at least a portion of *B*-cardiac myosin heavy chain DNA. Because of the use of the open claim language "comprising" and because the claim does not recite a purity or size limitation, the claim reads on the naturally occurring mRNA transcript of *B*-cardiac myosin heavy chain. mRNA transcripts are considered to be products of nature

and are not patentable. To overcome this rejection it is suggested that the claims be amended to include purity limitations which would distinguish the claimed compositions, as enabled by the specification, over the naturally occurring products. It is further suggested that such limitations include the terminology "isolated and purified" and/or a description of what the claimed products are "free of" relative to that of the natural source.

17. Claims 6, 13-23, 26, 37 and 38 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 26 are indefinite over the recitation of "small alteration" because the term "small" is relative and it is unclear as to what would constitute a small alteration and it is further unclear as to what is intended to be encompassed by an "alteration" in the DNA. That is, because there is no definition in the specification for "alteration" and because the claim does not clearly set forth a functional definition for alteration, it is unclear as to whether an "alteration" is intended to be limited to base mutations or is further inclusive of deletions and insertions and/or substitution of ribonucleotides, etc.

Claims 13-23 are indefinite over the recitation of "the disease" because this phrase lacks proper antecedent basis.

Claims 37 and 38 are indefinite over the recitation of "capable of amplifying" because capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. That is, it is not clear whether the recited primers have the potential to amplify or do in fact amplify the DNA. Amendment of the claim to read e.g. "...oligonucleotides which amplify" would obviate this rejection.

18. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d). Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,429,923. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '923 are inclusive of methods for diagnosing hypertrophic cardiomyopathy wherein the method comprises detecting the presence or absence of a hypertrophic cardiomyopathy associated mutation in the RNA of an individual. It is noted that the claims of '923 do not recite packaging the reagent required to perform the diagnostic method in a kit. However, reagent kits for performing DNA diagnostic assays were conventional in the field of molecular biology at the time the invention was made and therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the primers and probes required for the detection of hypertrophic cardiomyopathy associated-mutations in a kit for the expected benefits of convenience and cost-effectiveness.

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or

on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-31 and 36-38 are rejected under 35 U.S.C. § 102(a) as being anticipated by Rosenzweig et al (New England Journal of Medicine ((1991)325: 1753-1760).

Rosenzweig (p. 1754) teaches methods for diagnosing hypertrophic cardiomyopathy wherein the methods comprise the steps of isolating RNA from peripheral blood mononuclear cells, reverse transcribing *B*-myosin heaving chain RNA to cDNA, amplifying the cDNA by nested PCR and detecting the amplified *B*-myosin heaving chain nucleic acids using an RNA probe in a RNase protection assay in order to detect the presence of point mutations associated with hypertrophic cardiomyopathy. The reference further teaches 4 oligonucleotide primers for amplifying the *B*-MHC gene and RNA probes which are complementary to at least a portion of the *B*-MHC gene (see page 1754, col. 2). With respect to claim 23, the reference further teaches clinically evaluating the family members for symptomology associated with hypertrophic cardiomyopathy.

20. Claims 1-31 and 36-38 are rejected under 35 U.S.C. § 102(a) as being anticipated by Watkins et al. (New England Journal of Medicine ((1992) 326:1108-1114).

Watkins (p. 1109) teaches methods for diagnosing hypertrophic cardiomyopathy wherein the methods comprise the steps of isolating RNA from peripheral blood mononuclear cells, reverse transcribing *B*-myosin heaving chain RNA to cDNA,

amplifying the cDNA by nested PCR and detecting the amplified *B*-myosin heaving chain nucleic acids using a riboprobe in a RNase protection assay in order to detect the presence of point mutations associated with hypertrophic cardiomyopathy. The reference further teaches sets of nested oligonucleotide PCR primers for amplifying the *B*-MHC gene and RNA probes which are complementary to at least a portion of the *B*-MHC gene (see page 1109, col. 2). With respect to claim 23, the reference further teaches clinically evaluating the family members for symptomology associated with hypertrophic cardiomyopathy.

22. Claim 36 is rejected under 35 U.S.C. § 102(b) as being anticipated by Eisenberg (Journal Molecular and Cellular Cardiology (March 1991) 23:287-296).

Eisenberg teaches RNA probes complementary to the sequences of the *B*-MHC nucleic acids (see page 289). Accordingly, Eisenberg anticipates the invention of claim 36.

23. Claims 37 and 38 are rejected under 35 U.S.C. § 102(a) as being anticipated by Friedman (Basic Research Cardiology (March-April 1992) 87:106-112).

Friedman teaches sets of nested PCR primers useful for the amplification of nucleic acids of *B*-MHC (see page 109). Accordingly, Friedman anticipates the invention of claims 37 and 38.

24. Claims 37 and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Feldman (Circulation (June 1991) 83:1866-1872).

Feldman teaches compositions comprising sets of PCR primers useful for the amplification of nucleic acids of *B*-MHC (see page 1867). The compositions of Feldman contain 13 pmol of each primer and therefore are considered to comprise at least 4 oligonucleotides. Accordingly, Feldman anticipates the invention of claims 37 and 38.

25. Claims 24-30 are rejected under 35 U.S.C. § 102(b) as being anticipated by Almoguera (Current Communications in Molecular Biology (1989) pages 37-45).

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labelled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Accordingly, Almoguera anticipates the invention of claims 24-30.

26. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 33-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Rosenzweig or Watkins in view of the Stratagene Catalog.

Rosenzweig (p., 1754) and Watkins (p. 1109) each teach methods for diagnosing hypertrophic cardiomyopathy wherein the methods comprise the steps of isolating RNA from peripheral blood mononuclear cells, reverse transcribing *B*-myosin heaving chain RNA to cDNA, amplifying the cDNA by nested PCR and detecting the amplified *B*-myosin heaving chain nucleic acids using a riboprobe in a RNase protection assay in order to detect the presence of point mutations associated with hypertrophic cardiomyopathy.

The methods of Rosenzweig and Watkins each require the use of the reagents of primers for the amplification of *B*-MHC, riboprobes complementary to *B*-MHC DNA, and RNase to digest unhybridized RNA. Rosenzweig and Watkins do not teach packaging the reagents required to practice the detection method or instructions for the detection method in a kit.

However, reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers, riboprobe, and RNase in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art. With respect to claim 35,it would have been further prima facia obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit in view of the conventionality of including instructions in kits for facilitating the use of the packaged reagents. It is noted that the written material in the

instructions is not considered to be within the statutory classes and does not carry patentable weight (see MPEP 706.03(a)).

27. Claim 31 is rejected under 35 U.S.C. § 103 as being unpatentable over Almoguera in view of Mullis.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labelled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera does not teach amplifying the DNA by performing PCR using nested primers.

Mullis teaches the method of PCR and the amplification of this methodology for the detection or characterization of nucleic acids associated with genetic disorders (see col. 18). Mullis (col. 30) further teaches performing PCR using sets of nested primers in order to reduce the background in the amplification process and thereby increase the overall specificity of the amplification reaction.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Almoguera so as to have used

nested primers in the PCR amplification in order to have achieved the expected benefit expressly stated by Mullis of increasing the specificity of the amplification reaction and thereby of increasing the overall accuracy of the detection method.

28. Claims 1-7, 10-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Mullis.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. Geisterfer-Lowrance does not teach amplifying the sample *B*-MHC nucleic acid prior to determining the sequence of the DNA.

Mullis teaches methods for amplifying nucleic acids by the method of PCR and applies this methodology to assays to detect the presence of point mutations in nucleic acids associated with genetic diseases (see, e.g. col. 2, and 18). Mullis also teaches amplifying nucleic acids by PCR prior to sequencing (see column 36). The reference states that PCR provides the advantages of increasing the quantity of the target nucleic acid and thereby

increases the sensitivity of nucleic acid detection and characterization assays. Mullis further teaches that the presence of mutations associated with a disease can be detected in a sample RNA by first reverse transcribing the RNA to DNA, amplifying the DNA by PCR and then analyzing the amplified DNA for the presence of disease associated mutations.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have amplified the B-MHC nucleic acids prior to sequence analysis in order to have increased the quantity of the target DNA and thereby to have increased the overall sensitivity of the detection of hypertrophic cardiomyopathy associated point mutations in the *B*-MHC nucleic acids.

With respect to claim 12, Mullis (col. 30) further teaches performing PCR using sets of nested primers in order to reduce the background in the amplification process and thereby increase the overall specificity of the amplification reaction. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have used nested primers in the PCR amplification in order to have achieved the expected benefit expressly stated by Mullis of increasing the specificity of the amplification reaction and

thereby of increasing the overall accuracy of the detection method.

29. Claims 9 and 10 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Almoguera.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. Geisterfer-Lowrance does not teach detecting point mutations associated with hypertrophic cardiomyopathy by first amplifying sample *B*-MHC nucleic acids and performing a RNase protection assay.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labelled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies

single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera states that this provides a very rapid, efficient and sensitive means for detecting the presence of point mutations associated with diseases.

In view of the disclosure of Almoguera, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have detected the mutations associated with hypertrophic myocardiopathy in *B*-MHC nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay using a labelled RNA probe in order to have achieved the expected advantages of providing a more rapid, efficient, and sensitive assay for the detection of hypertrophic myocardiopathy associated mutations in *B*-MHC nucleic acids.

30. Claims 33-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Almoguera and further in view of the Stratagene Catalog.

The teachings of Geisterfer-Lowrance and Almoguera are presented above. Modification of the method of Geisterfer-Lowrance as discussed above would have resulted in a method for detecting point mutations in the *B*-MHC gene which required the use of the reagents of an RNA probe hybridizable to the *B*-MHC gene, PCR primers for the amplification of the *B*-MHC gene and a

RNaseA for digesting unhybridized RNA. It is noted that at the time the invention was made the complete nucleotide sequence of the B-MHC was well known in the art and therefore the generation of primers and probes to perform the amplification/RNase protection assay of Almoguera would have been obvious to one of ordinary skill in the art and well within the skill of the ordinary artisan. The combined references do not teach packaging these reagents required to practice the detection method or instructions for the detection method in a kit.

However, reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers, RNA probe, and RNase in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art. With respect to claim 35, it would have been further prima facia obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit in view of the conventionality of

including instructions in kits for facilitating the use of the packaged reagents. It is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight (see MPEP 706.03(a)).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for this Group is (703)-305-7401.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Carla Myers

May 7, 1996

Carla Myers

CARLA J. MYERS
PATENT EXAMINER
GROUP 1800